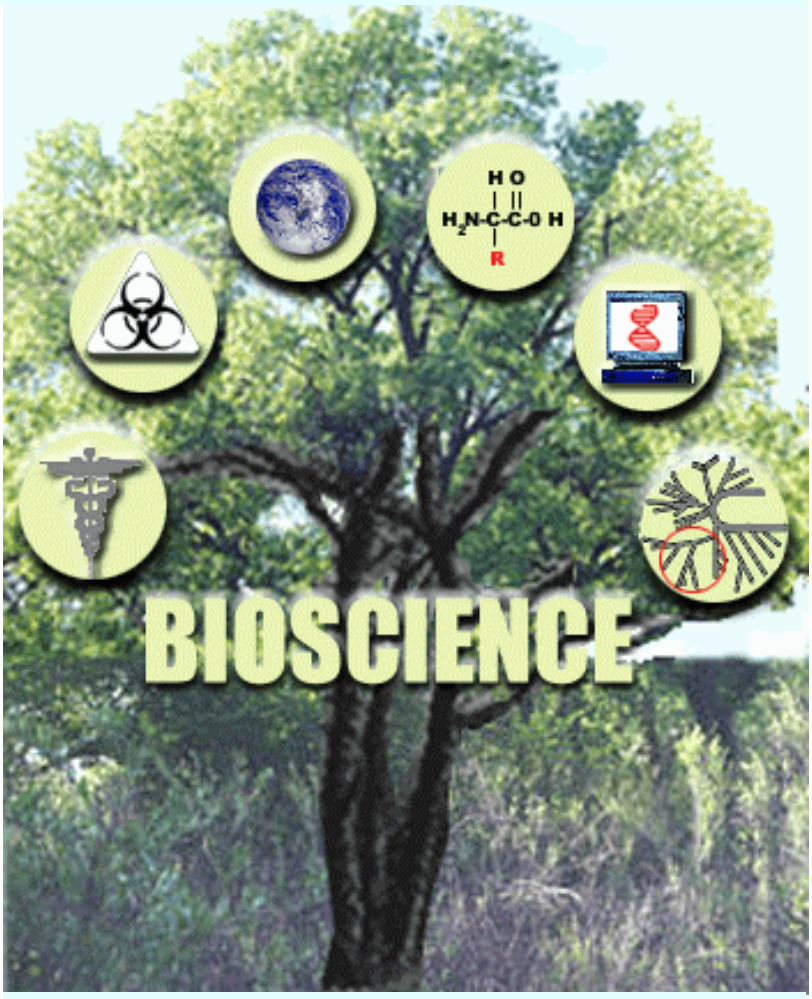
Bioscience Division

Laboratory Supporting Plan



2000-2002

Los Alamos

NATIONAL LABORATORY

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I. Vision and Mission

Our Vision

Innovation for health and security.

Our Mission

To create and discover frontier science and technology that benefits public health environment, and national security.

The 300+ research scientists, technical specialists, post doctoral researchers, students, and operations and administrative support professionals that make up Bioscience Division are focused on one of the most challenging scientific frontiers of 21st century; understanding and using biological complexity. The 20th century saw great advances in understanding biology. In the early 1900s we were still discovering what types of molecules made up cells. By the mid-1900s we had discovered the structure of DNA and understood that it stored the information needed to create the working units of cells; the proteins. The flow of genetic information from DNA to make RNA to make proteins developed into the central dogma of biology, and the biotechnology revolution was born. It became possible to sequence the entire genomes of organisms, such that we begin the 21st century with a complete draft sequence of the largest and most complex of genomes: the human genome. Los Alamos scientists played pivotal roles in first envisioning and then achieving this great accomplishment. And we pioneered the development and application of key technologies that have pushed forward on the frontiers of biology. Examples include the development of flow cytometry, the first DNA data bases and the tools that provided the basis for modern bioinformatics, stable isotope production and use in biomedical research. In this past decade, our scientists have pioneered the field of molecular forensics to serve our national security mission and to protect pubic health.

The convergence of biological, chemical, physical and computational sciences at this time in history provides us the tools to begin to unlock the secrets of the molecular machines and networks that operate within cells, and to use that knowledge to great benefit in national security, public health, and environmental applications. The Bioscience Division brings together a rich diversity of people, skills, science, technology, and cultures to continue to push on this most exciting frontier.

II. Our Guiding Principles and Management Model

Objective: To establish and grow a visionary, innovative scientific community that expects and fosters professionalism and commitment from its members.

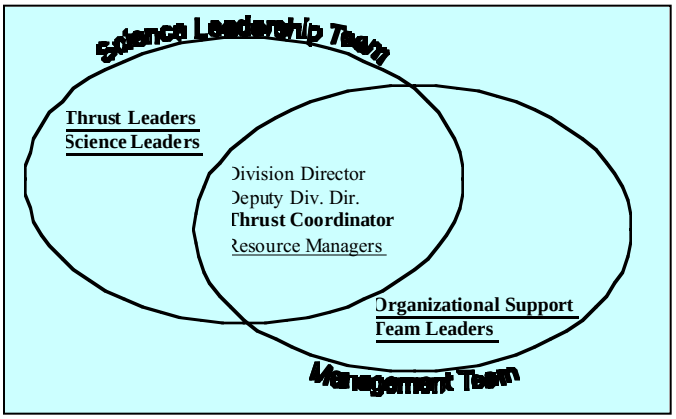
We will accomplish this by:

1. Making decisions within the bioscience community that are inclusive, interactive, and responsive.
2. Nurturing diversity in our science and our people
3. Anticipating and positively responding to change by being adaptive.
4. Creating scientific synergy in a relaxed atmosphere that motivates excellence.
5. Basing our interactions with one another on truth, integrity, and respect.

6. Building trust and confidence through teaming while encouraging individual freedom and initiative.

Bioscience Division uses modern management and business practices to provide an organizational framework that supports our science and technology goals in the context of our guiding principals. The Division is designed to operate in arenas that are fast moving and fast evolving, with a multi-disciplinary mix of science and technology, and geographically dispersed capabilities. The design incorporates flexibility and adaptability by facilitating easy to crosswalk between resources, capabilities, and thrust areas. Importantly, it also incorporates a social structure designed to recognize and draw upon the strengths of our scientific leaders.

Our structure utilizes a Science Leadership Team with a Management Team. In this structure we have combined a hierarchical management model with a flat participatory model. Operations and regulatory functions of the Division are worked within a hierarchical line management structure. Science leadership engages a flat team based approach with a greater emphasis on communication and relationship building. The Division Director, Deputy, Thrust Coordinator and Resource Managers serve on both teams to ensure that the science and management functions are worked in a coordinated way and are not in conflict.

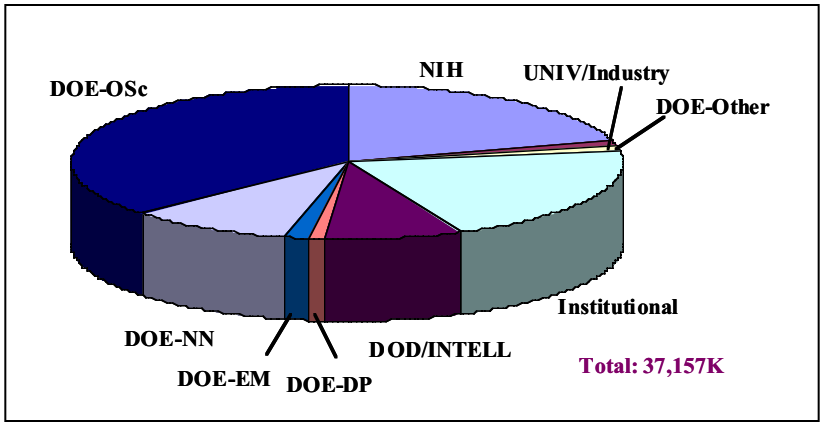


The Science Leadership Team is responsible for the development and implementation of the Division's strategic plan, and the management team ensures that our infrastructure, financial, workforce, communications subplans support our science and customer focused strategic goals.

For effective management of resources and personnel, we have organized the Division around three geographical locations. These "Resources" have selected names for themselves from historic scientific personalities that are identified with our science.

III. Our Core Programs

Our core program activities are supported by a diverse customer base and encompass programs/projects that vary dramatically in size from as small as $50K to as large as $10 million. The Center for Human Genome Studies is our largest program, and works on human genome sequencing as a member of the Department of Energy's Joint Genome Institute. The DOE Office of Science (OSc) also supports smaller programs in our division in health effects, DNA damage and repair, structural biology, functional genomics, biomedical sensor development, phylogenetic analysis of genomes, and stable isotope labeling



technology development using biosynthetic approaches. We also have a strong program supported by the DOE Chemical and Biological Non-Proliferation program focusing on the biological foundations and detection of biological threat agents. The FBI and intelligence community also supports our work in the area of detection and forensics in relation to bio-threats. A large number of our investigators have individual investigator initiated R01 awards that provide a core fundamental science base that, along with Laboratory Supported Research and Development funds, provides us with flexibility and in a number of cases the seed money to develop entire new areas. In addition to the individual investigator awards, we have two NIH Research Resources that serve the broad biomedical research community (the Stable Isotope Research Resource and National Flow Cytometry Resource). Our NIH and LDRD work often leverages of capabilities and expertise developed to support work done for our principal DOE sponsors. Finally, we have strong efforts in materials chemistry, synthetic chemistry, and inorganic chemistry supported by a variety of sponsors for work further the frontier of those disciplines as well as their applications in bioscience.

IV. Our Strategic Thrusts

This set of future thrusts represents the areas we have targeted for significant expansion on the 2-5 year time scale. The thrusts range in scope from being targeted at very specific and finite funding opportunities (the Structural Genomics thrust) to an emphasis on extensive capability strengthening and "market analysis" to determine the appropriate niche for B division and the Laboratory (the Complex Biosystems Modeling thrust). The Division has identified a scientific leader for each thrust and each leader has in turn recruited a team to work on a strategic plan for that thrust. Thrust Leaders are supported for up to 25% of their time to focus on this task. Our thrust plans are living documents. At the time of this writing, work is focusing on integrating the thrust plans with our work force plan. Our six future thrusts are:

1. Biothreat Reduction Science and Technology
2. Functional Genomics
3. Structural Genomics
4. Natural and Engineered Biochemical Diversity
5. Biomedical Technology
6. Complex Biosystems Modeling

1. Biothreat Reduction

Goals. Develop biological and genetic foundations for threat reduction technologies, organize and apply this information.

Summary

Our planet is threatened with increasing emergence of infectious disease from new, naturally evolved antibiotic resistant and more virulent strains of bacteria or viruses. We can add to this concern the increased concern of deliberately introduced biological agents that might be naturally occurring pathogens or genetically modified reagents for which no effective therapy yet exists, by rogue nations or terrorist groups that are designed to target human populations, crops and agricultural livestock.

Our Biothreat Reduction thrust focuses on three approaches:

- Genetic and molecular characterization of biological threats and developing an understanding of host-pathogen interactions;

- Molecular and immunological methods that detect threat pathogens and design pathogen countermeasures; and

- Next-generation biosensor tools and field instruments based on new knowledge acquired.

Bioscience Division's extensive experience in DNA-based pathogen detection methods, bioinformatics tools, characterization of complex environmental samples and instrument development helps place the Laboratory in a position to establish a lead role in the development of biothreat reduction technologies.

Customer/funding outlook
The largest proportion of funding currently comes from the DOE Chemical and Biological Non Proliferation (CBNP) program. Additional sponsors include the US Army (USAMRID), the Defense Threat Reduction Agency (DTRA) and to a lesser extent the NIH and the CDC. CBNP funding is expected to grow, as is interest from the military and intelligence communities. Fundamental research is likely to be supported by NIH, DOE and NSF.

Capability Mapping
This thrust draws on all the capabilities in B division.

2. Functional Genomics

Goals: Discover gene function through the development and use of genome-scale high throughput and computational approaches.

Summary
With the completion genome sequencing of whole organisms, chromosomes, and ultimately human, plant and animal genomes, we can now turn to the study of how the products of these genomes collectively function in complex environments. Such research requires the merging of information about gene and protein sequence, regulatory mechanisms, biochemical and biophysical structure and function data and the complex interactions of biomolecules with nucleic acid and protein networks. Thus, Functional Genomics will be a systems biology research of how genes and their products operate in the context of the whole cell and indeed the whole organism.

The specific goals of the Functional Genomics thrust are:

- Develop genome-scale, high-throughput experimental and computational approaches to functional genomics,
- Provide a functional genomics resource that is of wide, long-lasting value to the broader medical and scientific community and
- Utilize our capabilities in Functional Genomics to address national and international problems that are relevant to human health and the environment.

Customer/Funding Outlook
A major initiative from DOE termed the "Microbial Cell Project," represents an effort that seeks to understand the complexity at the level of a whole organism, in this case starting first with a simple microorganism as a model. Genes and their variations and how they contribute to disease or protect from disease are areas of investigation of great importance and the subject of potential NIH programs. The potential exists for a national Functional Genomics Repository supported by NIH to offer knowledge gained from microbial and human cell projects to scientific investigators. The DOE/CBNP program and HHS are increasingly focusing on bio-threat issues and increased funding in this arena will lead to new opportunities in the area of host-pathogen genomics.

Capability Mapping
Measurement Science & Diagnostics, Genomics and Molecular Biology, Computational Biology, Molecular Synthesis; Structural Biology.

3. Structural Genomics

Goals: Create a comprehensive view of protein structure through the development and application of high throughput and computational technologies that will allow the prediction of structure and function from sequence.

Summary
Structural genomics is a new and rapidly developing field in biology. The goal of this field is to discover and analyze the structures of nearly all protein molecules in nature in order to provide a foundation for a fundamental understanding of biology at the molecular level. These three-dimensional structures of proteins will be important in rational drug design for pharmaceutical applications, in catalysis for the chemical and biotechnology fields, and in diagnosis and treatment of genetic disorders using molecular medicine. Structural genomics is closely tied to functional genomics, the identification of functions of all proteins in nature, and to genomic sequencing, the determination of the genetic blueprints of all organisms.

Customer/Funding Outlook
NIH (Pilot project Centers, technology development, planned total distributions $20M/year); DOE (technology development, total distributions $2M/year); Follow-on larger scale funding from NIH/DOE, pharmaceutical companies; DOE and DOD threat-reduction funding.

Capability Mapping
Molecular & Cellular Biology; Computational Biology; Structural Biology; Genomics and Molecular Biology.

4. Natural and Engineered Biochemical Diversity

Goals: Discover, create and characterize the diversity of biochemical mechanisms for technology applications.

Summary
There is wide recognition that only a relatively small fraction of the microbial species in the biosphere has been discovered and cultured. Further, there are still large numbers of new species of plants and microorganisms being discovered every day, with metabolic capabilities and biochemical conversions that are simply not found in animals or humans. The important potential of the diversity in catalytic function (enzymes) present in plants and microbes is receiving worldwide attention. For example, at least three major U.S. chemical companies (Dupont, Dow, and Monsanto) have shifted the focus of their development activities from chemical catalysis, to biocatalysis and biotechnology. Potential applications for this thrust area include:

- Reduction of global warming through carbon sequestration technologies that prevent carbon from being released into the atmosphere;
- Development of alternatives to the combustion of fossil fuels, e.g., bio-based fuels and chemicals; enzyme engineering for biocatalysis;
- Understanding function in microbes; and
- Biomimetic materials.

The overarching strategy for this thrust is to bring together multiple disciplines to develop new analytical technologies for biomedical research, disease detection, and health monitoring and bio-threat detection.

Customer/Funding Outlook
Though small in scope, DOE Basic Energy Sciences has had a mission to examine bio-based sources of energy. DOE/FE (Fossil Energy) and DOE/EE are sources of new funds in this arena, as is the Chemical Sciences Division within DOE/BES. Industry is also an important potential customer here and Los Alamos has a good deal of experience in industrial interactions in this domain**..**

Capability mapping
Biologically Inspired Materials and Chemistry; Computational Biology; Environmental Biology, Molecular Synthesis. Molecular & Cellular Biology, Structural Biology, Genomics.

5. Biomedical Technology

Goals: Bring together multiple disciplines to develop new analytical technologies for biomedical research, disease detection, and health monitoring and bio-threat detection.

Summary
The Biomedical Technology thrust is a focused effort to develop and apply new sensor technologies, physical techniques and devices for biomedical research, disease detection and disease monitoring, and bio-threat agent detection. Examples include, but are not limited to, optical techniques for disease detection that employ spectroscopy or sensors that invoke molecular recognition and sensitive fluorescence detection *in situ* or in single cells. The technological advances are the result of collaborations that bring biologists and chemists together with physicists and engineers.

Customer/Funding Outlook
Biomedical engineering is the focus of a new National Institutes of Health Initiative through a new multi-institute program, the Biomedical Engineering Consortium (BECON). Several calls for proposals have been announced for proposals at the interface of biology, chemistry, physics and engineering. Funds are set aside for supporting single investigator awards as well as for Bioengineering Research Partnerships that can be as large as $2M per year.

Capability mapping
Medical Applications, Measurement Science & Diagnostics; Supramolecular Assembly; Molecular Synthesis; Biomimetics and Chemical Modeling, Computational Biology.

6. Complex Biosystems Modeling

Goals. Create, validate and apply new models for complex biological systems, e.g., molecules, macromolecular complexes, a cell, an organ, disease ecology and large community dynamics.

Summary
A growing challenge across the range of Bioscience Division programs and thrust areas is the need for complex biosystem modeling; this need will dramatically increase in the years ahead. Bioscience Division is already recognized for its outstanding development of research databases and annotation of DNA sequences, and epidemiological information on pathogenic organisms and influenza viruses. This thrust seeks approaches that will capitalize on and add to our expertise to be able to address such issues as, regulation of gene expression, polymorphism analysis, phylogenetic analysis, prediction of RNA and protein structure, and prediction of protein function and interactions. Implementation will require development of new large and complex databases, methods for predicting specific DNA-protein interactions, and extensive modeling of regulatory systems that could rapidly come to tax our teraflop computers as more complex networks and structural interactions begin to be understood.

The Complex Biosystems Modeling thrust is effectively a "plan to plan", which is based on our recognition that computational biology has not reached a critical mass and is in critical need of developing long-term leadership and direction.

The ***specific goals*** for this thrust focus on training and recruitment; training includes cross-training for lab individuals thus recruiting established personnel into a discipline/career change. Workshops and conferences are also envisaged.

Customer/funding outlook
An important distinction must be made between customer and sponsor in the context of this thrust. Analysis shows that the capabilities of computational biology and bioinformatics underpin many if not all of the other thrusts, thus we define "customer" in this case to be clients of the work to be accomplished under the auspices of this thrust (e.g., other projects/thrusts/programs at LANL, the external scientific community) and "sponsor" as the likely sources of funding. NIH, DOE, DOE CBNP, DOD CDC are each potential sponsors for future activities in this thrust. NIH currently has a significant call out for Centers of Excellence P-50 (and P-20 Planning) proposals.

Capability mapping
Almost by default, Complex Biosystems Modeling maps to all of B Division's capabilities.

V. Our Core Capabilities

Introduction
The Bioscience Division incorporates nine broad science and technology capabilities. These capabilities support core program activities and provide the foundation for our future thrusts. They have both unique characteristics and five unifying or common characteristics. The unique characteristics of each capability can be found within the definition of each. Unifying characteristics which are descriptors common to all the capabilities include technique development, high throughput assays, simulation,
multidisciplinary approach, and complex systems.

- **Biologically Inspired Materials and Chemistry**; includes biocatalysis, biomimetics, biomaterials, biopolymers, inorganic, organic, and hybrid materials, materials characterization, model chemistry, modeling, soft materials and polymers
- **Computational Biology**; includes 2-D and 3-D biomaterials modeling, bioinformatics and theory, biothreat data annotation, computational biomechanics, computational structural biology, database development and inter-operation, data minding, knowledge-based optimization, simulation modeling, statistics, and web portal development. B Division has a highly developed bioinformatics capability as part of Human Genome Project.
- **Environmental Biology**; includes archeo- and exo-biology, disease ecology, environmental chemistry, microbiology (environmental and general), geochemistry, microbe functions in the environment, microbial diversity, nucleic acid isolation and purification, pathogen microbiology, plant and microbial physiology.
- **Genomics**; includes DNA sequencing, functional genomics, genomic mapping, high throughput assays, mass spectrometry, microarrays, molecular epidemiology, phage display/recognition ligands, robotics/automation, threat agent detection and sequencing.

- **Measurement Science & Diagnostics**; includes capillary electrophoresis, flow and image cytometry, detection, attribution, and analysis, hyperspectral imaging, imaging and microscopy, molecular spectroscopies, sensors, and single molecule detection.
- **Medical Applications**; includes advanced optical imaging, diagnostic instrumentation, eye modeling optical spectroscopy radiolabeled peptides, SNP assays, and therapeutic instrumentation.
- **Molecular Cell Biology**. Includes 3-D spheroid models, biochemistry and enzymology, enzyme metabolism, health effects, genetics, proteomics.
- **Molecular Synthesis**. Includes biosynthesis, chiral synthesis, protein expression and purification, organic chemistry, recognition ligands (biomimetics, antagonists), medical and stable isotope labeling.
- **Structural Biology**. Includes crystallography, structural dynamics, modeling and simulation, neutron and x-ray scattering, NMR spectroscopy, optical and vibrational spectroscopies, protein engineering.

VI. Operational Goals

Bioscience division supports the laboratory's and the SSR directorate's commitment to demonstrate consistent operational excellence, in our business operations, our facility management, our approach to safety and security management, and our commitment to revitalize our facilities.

Our ***primary operational goals*** currently are:

- Install consistent safety, security and (where applicable) facility management practices across the full geographic dispersal of the division. This effort involves negotiating good, tight tenant agreements with a number of FMUs and managing our own FMU in that context (FMU72).

- Have a comprehensive plan for continued improvement of our existing infrastructure to meet new programmatic goals. This plan is fully developed and has a team leader (Julie Wilson) assigned to continue its development and implementation (latest draft June 2000).

- Commence development of a case for combined revitalization and risk mitigation of our facility through a new, third-party financed building. This effort has a complete business plan developed in partnership with PM-1 (document PM-1:00-28).

- Evaluate and potentially establish BSL-3 designation within B division. This planning effort has included developing a design for such a facility and a comprehensive communications plan to engage the SET, the workforce, and the public in evaluating the proposed project and its impacts. This communications plan has been developed with the help of PA.

- Safely and responsibly steward full recovery from the effects of the Cerro Grande Fire

VI. Workforce Goals

Our ongoing Workforce Development Plan is examining:

- The health and vitality of each of our capabilities.

- Emerging areas of need (particularly with respect to our thrusts).
- Our competitive position (strengths and weaknesses).
- Workforce requirements by capability and cross-mapped to strategic thrusts.
- Recruiting and retention policies and principles at all staff levels, from student to senior level TSM.
- Succession plan for both key scientific positions and all leadership positions.
- Employee development and mentorship practices both during immediate post-hire evaluative phase and long term, again at all staff levels.
- Our succession plan for management, science leadership, and all employment series.

Our ***goal*** is to have a comprehensive workforce plan completed by October 31, 2000.

VII. Communication Goals

The Bioscience Directorate supports the Laboratory and SSR objective to be increasingly valued as a good neighbor. The Division will, with the assistance of the appropriate laboratory support, e.g. Public Relations and Community Outreach staff maintain a candid, open and effective relationship with the community.

We have a communications team (team leader Sandra Zink) that has developed a comprehensive internal communications strategy that is implemented. We also have a team working on community projects focused around informing the community about what we do, and there are a range of educational outreach activities. We are also developing a course to be held at UNMLA on Modern Biology.

We have a number of ***specific goals*** in our communications plans:

- Two-way communications with our workforce in a way that ensures we receive input and communicate decisions in an open and timely manner. This goal is aided by all-hands meetings, the B Scene (a biweekly internal publications), news from Jill's desk emails (weekly), Resource meetings, and management walk arounds.

- Ensuring that we are informing our workforce and communities about all our activities in an open and timely manner, particularly in the areas of public health and biothreat reduction.

- Developing a communications plan that will help guide the public discussions that are important before we embark on any plans toward establishing a BSL-3 capability.

- Developing a communications plan that addresses the issues associated with our plans for a new Bioscience Division Building.

VIII. Financial Goals

In its first few months of operation, B division, a predominantly experimental division achieved and set an overhead rate equivalent to that of T-division, a predominantly non-experimental based division. Our ***first goal*** is to adhere to and improve upon that benchmark.

We are committed to fiscally responsible and accountable management practices. It is our ***goal*** to establish a budget/procurement team dedicated to B Division's needs. We expect to plan for and achieve this transition in the coming year.

We plan for continued expansion of the overall B Division budget at a rate of 8% per year. The increased budgets are anticipated to be mostly in the thrust areas.